Cancer Biology and Control of Cell Growth.

Faculty: Bitterman, Hecht, Henke, Kratzke, Lange, Murphy, Van Ness

This theme draws together investigators whose interest range from cancer to lung fibrosis. Understanding the control of cell population size and its principal determinants: motility, proliferation and cell death are longterm foci for collaborations in training and research. In vitro studies of lung cells and cancer cells complement in vivo studies of genetically engineered mice. Trainees learn fundamental skills essential to mechanistic studies of lung development and lung repair. The University’s Stem Cell Institute has been a longstanding strength and Jakub Tolar MD, PhD, Associate Professor of Pediatrics, is its new leader. Many T32 faculty are members of the UMN NIH Comprehensive Cancer Center. Recently collaborative work on lung cancer has expanded, including Drs. Bitterman, Kratzke and Wendt. Drs. Lange and Murphy, bring additional expertise in cell signaling and the role of nicotine.

Dr. Peter Bitterman, Professor & Vice-Chair of Medicine; Associate Director, MD-PhD Program

Translational Control of Cell Fate: We seek to understand how the activity of the protein synthesis apparatus regulates cell fate and function. We discovered that pathological activation of translation initiation complex eIF4F imparts cells with autonomy for growth and survival and is required for cancer cells to maintain a malignant phenotype. In contrast, inhibition of eIF4F function activates apoptosis in these cells without harming normal cells. This laboratory addresses 3 major questions: 1.) What steps in the process of translation initiation are integral to the regulation of proliferation and apoptosis? These experiments utilize genetic modulation of the translation initiation apparatus to pinpoint critical amino acid residues required for apoptosis regulation in cardiac, respiratory and cancer models. 2.) Which specific mRNA species encoding master regulatory proteins are subject to translational control? We use novel microarray and informatics procedures that we have developed to decipher the encrypted rules governing the translational control step in the flow of genetic information. 3.) Can we therapeutically target the protein synthesis apparatus with small organic molecules designed to eliminate autonomy of cancer cells or fibroblasts in fibrotic cardiac, vascular and pulmonary lesions? With Dr Wagner we developed high throughput techniques to test novel translational repressors as potential anti-cancer and anti-fibrotic agents.

Colin Campbell, PhD, Associate Professor of Pharmacology

Genetic Mechanisms of DNA Repair in Cancer: My laboratory studies the molecular genetic mechanisms of DNA repair and recombination in mammalian cancer cells with the goal of identifying genes that play important roles in this process. We also seek to determine the protein products of the genes for catalysis of DNA repair. Our longer range goal is to therapeutically intervene to prevent cancer cells from repairing their DNA and thereby increase their susceptibility to treatment.

Stephen Hecht, Ph.D, American Cancer Society Professor; Wallin Chair in Cancer Prevention

Mechanisms of Tobacco Carcinogenesis: The focus of the Hecht laboratory is mechanisms and prevention of tobacco-induced cancer. Research focuses on the metabolism, DNA binding, and carcinogenicity of important carcinogens in tobacco smoke believed to be involved in lung cancer etiology: polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, and certain volatile organic compounds including formaldehyde, acetaldehyde, and acrolein. One major goal is to develop metabolism-based or DNA-based biomarkers to predict lung cancer susceptibility in smoking, facilitating preventive approaches.

Craig Henke, MD, Professor of Medicine

The IPF fibroblast phenotype: Our goal is to understand the pathogenesis of Idiopathic Pulmonary Fibrosis (IPF), a lethal, progressive fibrotic lung disease without effective therapy. We seek to identify the source of disease-mediating IPF fibroblasts and identified the presence
of pathological mesenchymal stem cells (MSCs) that give rise to pathologic progeny. My lab is characterizing the IPF MSCs and delineating the mechanism(s) by which they differentiate into disease-mediating fibrotic fibroblasts. We also want to understand the role of the IPF fibrotic matrix in regulating the differentiation of IPF MSCs to IPF fibroblasts. We also are defining how the collagen-rich extracellular matrix regulates lung fibroblast function through integrin-collagen interactions to define the upstream components of the integrin signaling pathway that may be molecular targets for IPF treatment.

Robert Kratzke, MD, Associate Professor of Medicine

Genetic Abnormalities in Lung Cancer: My research centers on molecular abnormalities that underlie lung cancer and mesothelioma. We study the loss of function of cell cycle regulatory genes in these cancers. With thoracic surgery colleagues, studies on detection of micrometastases and their acquired molecular abnormalities are in process.

Carol Lange, PhD,* Professor of Medicine and Pharmacology

Hormone Receptors and Kinase Signal Transduction in Cancer: My lab uses human cell line and mouse models to understand mechanisms of breast, lung and ovarian cancer progression that involve signal transduction cross talk with steroid hormone receptors. My expertise is signaling pathways upstream of mitogen-activated protein kinases (MAPKs) and the role of mitogenic protein kinases as major inputs to ligand-dependent and independent progesterone receptor action and target gene selection. I also study the roles of breast tumor kinase (Brk/PTK6) actions upstream of the ERK5 and p38 MAPK stress signaling pathways in tumor progression. Previously I studied hormone receptors in lung cancer and am excited to develop parallel projects in this area, targeting signaling molecules as part of combination therapies to halt tumor progression and metastasis.

Sharon Murphy, PhD,* Professor of Biochemistry, Molecular Biology & Biophysics, DGS BMBB

Metabolism of Nicotine and Nitrosamines: Since nitrosamines are strikingly tissue specific in regard to their tumor induction, my lab characterizes the extrahepatic cytochrome P450 enzymes that activate nitrosamines. For example cytochrome P450 2A13 is highly expressed in human lung and is a very efficient activator of nitrosamines to the tobacco carcinogen NNK. We also examine enzymes involved in nicotine metabolism and are determining whether differences in enzymatic pathways accounts for the more than 4 fold differences in lung cancer risk across ethnic groups.